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METABOLIC STUDIES ON NEOPLASM OF BONE WITH THE AID OF RADIOACTIVE STRONTIUM*

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Chemical and spectrographic studies regarding the mineral composition of the animal body have revealed the presence of "trace" amounts of strontium in living tissue. Stoeltzner[9] has reported the first description of this by König in 1874 and her own experiment of feeding dogs with strontium. She found a selective uptake in the spongiosa and in the epiphyseal regions of the bones. Growing animals which were maintained on a diet low in calcium and in which the normal calcium requirement was replaced by strontium developed toxic symptoms clinically resembling rickets. The strontium-fed animals showed a considerably higher amount of water-soluble alkaline earth content in the bones than is found in rickets, and therefore a biochemical difference between the two elements was apparently demonstrated. Lehnerdt[4] found that a part of ingested strontium was excreted in the milk. He also found a considerable amount in the bones of suckling young. According to McCollum,[5] Wheeler (loc. cit.) found that strontium was capable of replacing calcium to a considerable extent in the eggshell and in the bones. Shipley (loc. cit.) and coworkers pointed out that this mineral cannot replace calcium in normal *bone formation*. Kenney and McCollum (loc. cit.) confirmed these observations. Drea (loc. cit.) showed that strontium is one of the elements which pass from the food and water into the hen's blood and egg, and then into all of the tissues of the embryo.

The cyclotron (Lawrence *et al.*[3]) has made available a supply of the radioactive isotopes of calcium ($_{20}Ca^{45}$) and strontium (Sr^{89}). By means of these Pecher[1,6a,7] was able to resolve the results of classical investigations into a quantitatively accurate formulation of the exchange of calcium and strontium. He found that:

1. Of a dose of radioactive calcium, 58% was recovered from the skeletons of mice after 24 hours. Of a dose of radioactive strontium, 33% was similarly recovered.[6]

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2. In the case of both radioactive strontium and radioactive calcium the activity of the skeletons of mice indicated that nearly maximum uptake was reached 8 hours after intravenous administration.[6]

3. Bone uptake of radioactive calcium and radioactive strontium was nearly three times as great following intravenous administration as that following oral administration.[6]

4. Radioactive calcium and strontium originally fixed in the skeletons of mice was found to migrate to the fetuses during the last days of pregnancy and to be transferred to offspring through lactation.[7]

5. Radio-strontium administered intravenously to lactating cows was recovered in the milk in the amount of about 10% of the dose, during the first 4½ days following administration.[1]

The demonstration of the selective localization of calcium and strontium in bone has suggested strongly the application of the radioactive isotopes of these minerals to clinical metabolic studies and possibly to therapeutic bone irradiation. Because of its relatively greater availability radioactive strontium has been selected for this purpose. Pecher[illegible] has reported clinical and postmortem studies with radioactive strontium on a group of cases of carcinoma with demonstrated bone metastases.

Figure 1 demonstrates the method of treatment usually employed in these cases. Response of the red blood cell level is shown. The lowering of the phosphatase* value and its maintenance at a point only slightly above the normal limit over a considerable period of time is also indicated.

The recent work of Woodard and Higinbotham[10] has demonstrated high phosphatase values in osteogenic tumors. In many such cases the phosphatase activity of the tissue is reflected in elevated values for serum phosphatase. These authors have also shown that inactivation of such tumors by external irradiation results in lowering the phosphatase activity of both the tumor and the serum. These facts, together with the demonstrated reduction of serum phosphatase activity by the administration of radio-strontium in the case cited above, suggested the possibility of a high uptake of strontium by osteogenic tumor tissue. The selective uptake of radio-phosphorus (P^{32}) in soft tissue tumor cells has been shown by Jones, Chaikoff and Lawrence[2] to be greater than in any other type of soft tissue. A parallel between this behavior and that of radio-strontium in osseous tumors would appear to be probable. Therefore, it has seemed desirable to investigate the metabolism of tumors of the bone with the aid of radio-strontium. Accordingly, small doses of radioactive strontium have been administered to

* Phosphatase activity was estimated by the method of Bodansky (J. Biol. Chem., 99, 197, 1932; 101, 93, 1933) for the determination of alkaline serum phosphatase activity.

6 such cases, prior to biopsy or amputation, and the tissues have been assayed to determine uptake. The following is a report of these investigations.

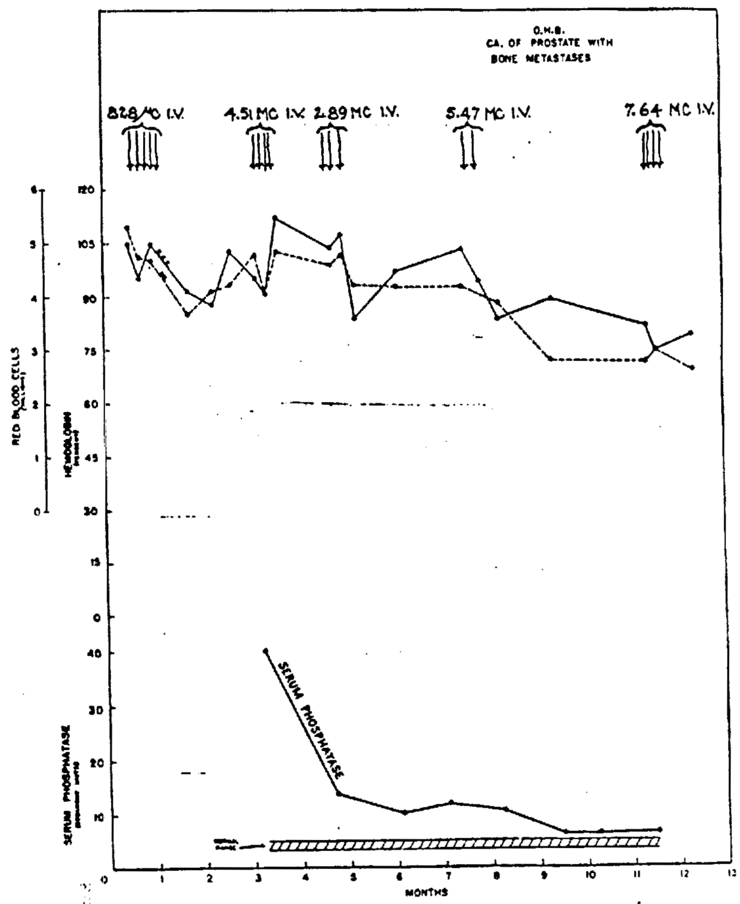


FIG. 1.—Carcinoma of the prostate with bone metastases: response of serum phosphatase, hemoglobin and red blood cell levels to radio-strontium therapy. (Arrows indicate fractioning of total doses shown.)

Methods. 1. Radioactive strontium, first described by Stewart, Lawson and Cork,[8] was prepared in the Berkeley 60 inch cyclotron by bombardment of metallic strontium with 16 million volt deuterons.

2. Tissues for assay were reduced to aliquots of approximately 1 gm. wet weight and ashed at 400° C.

3. Ashed samples were assayed for radioactivity on a standardized Du Bridge electrometer or a Geiger counter and compared with a uranium standard.

Results. CASE 1. [redacted] 17-year-old white male school boy, weight 130 pounds, entered the University Hospital May 15, 1941, complaining of constant pain in the right hip. Past history revealed that the patient had fallen on his right hip 6 months earlier without immediate serious after-effects. In April the patient noticed that the right thigh was longer than the left and that he was limping. Swelling over the right femoral trochanter and upper portion of the right ilium had developed, and he had lost 15 pounds.

The family history shows that 1 brother died at the age of 7 years of osteogenic sarcoma following the fracture of the right femur. Another brother died at the age of 12 years of carcinoma of the colon.

The roentgenogram showed a large soft tissue mass with calcification arising in the right ilium and spicules radiating from it, the typical appearance of osteogenic sarcoma. A biopsy resulted in the diagnosis: chondrosarcoma (osteogenic sarcoma).

On May 20, 1941, 1462 μc. of radio-strontium was administered intravenously, and on May 29 a second biopsy was taken.

The tissues were assayed with the following results:

Tissue	Radio-strontium uptake, μc./gm.	%/gm. tissue of dose
Muscle (normal?)	0.1475	0.010
Fat	0.00663	0.00045
Bone (apparently uninvolved)	0.244	0.0166
Bone and marrow	0.1948	0.0131
Bone (infiltrated)	0.498	0.034
Tumor	0.361	0.0246
Blood clot	0.0684	0.0046
Skin (normal)	0.342	0.0223

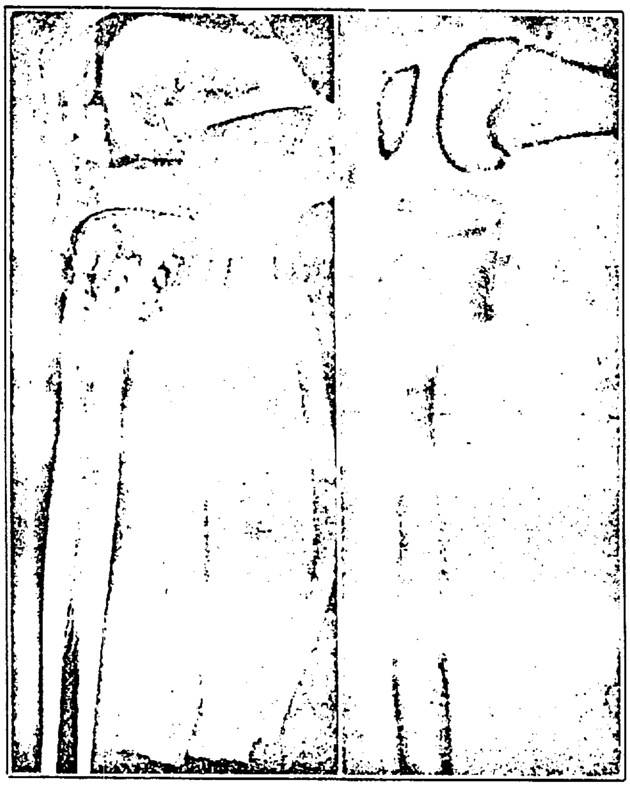
CASE 2. [redacted] a 27-year-old white male, weight unknown, was admitted to the University Hospital in April, 1941. Past history showed that he had a spiral fracture of the right femur in 1937. One month later a roentgenogram of the knee joint revealed a tumor involving the external condyle. This was diagnosed radiologically as a giant cell tumor. No biopsy was made at that time.

The patient was treated with Roentgen ray, and the area became more dense and quiescent. In February, 1941, a tumor was noted involving the lower third of the thigh. Roentgen ray examination revealed a chiefly extracortical tumor showing elevation of the periosteum and small "specks of calcification within the tumor." On Roentgen ray films taken in April, 1941, the tumor still appeared to be extracortical. The old fracture line was still discernible. Radio-strontium (1183 μc.) was administered *orally* April 29, 1941, at 11 P.M. Amputation was performed April 30, 1941, at 12.30 P.M. Microscopic examination resulted in the diagnosis: osteoblastic osteogenic sarcoma of the femur.

Tissues were assayed with the following results:

Tissue	Radio-strontium uptake, μc./gm.	%/gm. tissue of dose
Skin	0.0064	0.00054
Fat	0.00361	0.0003
Muscle	0.0036	0.0003
Femur	0.0131	0.0011
Marrow	0.0094	0.00079
Tumor	0.0073	0.00061

CASE 3. [redacted] a 13-year-old white male student (weight 107 pounds), entered the University Hospital on June 24, 1941, because of gradual onset of pain and tenderness associated with pressure of a tumor mass in the upper right tibia region. Past history revealed that he was perfectly well



a b

FIG. 2.—a. Roentgenogram of section of leg (Case 3). b. Autoradiograph of section of leg (Case 3), showing concentration of Sr_{89} in tumor and at epiphyseal line.

until 7 weeks previously, at which time he was struck in this region by a soft baseball. The immediate pain subsided after a few days only to return about 1 week later and gradually to progress. The patient was then hospitalized. Temperature on entry was normal. There was a rather diffuse, egg-sized swelling over the antero-medial aspect of the upper end of the right tibia with some increased local temperature, moderate tenderness to pressure, and dilation of the superficial veins. There was no lymphadenopathy. Biopsy (June 26): osteogenic sarcoma. Radio-strontium (357 μc.) was administered intravenously July 2, 1941. Amputation was performed on July 7, 1941.

Figure 2 shows the roentgenogram and autoradiograph of the section submitted for activity assay.

Tissues were assayed with the following results:

Tissue	Radio-strontium uptake, μc./gm.	%/gm. tissue of dose
Femur spongiosa	0.0066	0.0018
Femur epiphyseal line	0.106	0.029
Cartilage (femur epiphysis)	0.0318	0.0088
Bone with tumor (front)	0.1461	0.041
Bone with tumor (back)	0.1586	0.044
Muscle	0.0052	0.00146
Fat	0.0002	0.00005
Tumor	0.0996	0.0279
Skin	0.0772	0.0215
Femur cortex	0.0542	0.015

CASE 4. [redacted] a 9-year-old white female (weight 85 pounds), was admitted to the University Hospital February 21, 1941. About 3 months prior to admission a small hard swelling was observed over the distal portion of the ventral surface of the right forearm. This was not painful and did not appear to be inflamed. The motion of the wrist was not restricted. There was no history of trauma or injury. A Roentgen examination was made, and a diagnosis of bone tumor resulted. On a biopsy, the diagnosis of Ewing's tumor of the radius was established. A series of Roentgen ray treatments was instituted immediately over the extremity and the chest, and the local mass disappeared almost completely. Roentgen examination, however, still revealed evidence of a tumor in the right forearm. Pain had developed during the 3 weeks prior to this examination. At the time of admission there appeared to be no abnormality in the contour of the right forearm, by observation or palpation. There was no tenderness. About 9 months after the first admission the patient returned because of a rapidly increasing mass involving the right forearm. There was no tenderness except on very firm pressure. Roentgen examination revealed a definite increase in the tumor mass involving the right radius so that the entire shaft was then involved. There was extensive invasion of the soft tissues. No metastasis to the lungs was demonstrated. Radio-strontium (326 μc.) was administered intravenously September 25, 1941. Amputation was performed September 30, 1941.

Tissues were assayed with the following results:

Tissue	Radio-strontium uptake, μc./gm.	%/gm. tissue of dose
Cortex of ulna (normal bone)	0.032	0.0098
Epiphyseal lateral humeral condyle (normal)	0.02442	0.007
Tumor, sample 1 (of radius)	0.0106	0.0032
Tumor, sample 2 (of radius)	0.0122	0.0033
Fat	Trace	
Muscle	Trace	
Skin	Trace	

CASE 5. [redacted] a 54-year-old white male (weight 131 pounds), was admitted to the University Hospital August 22, 1941. About 18 months prior to admission the patient had developed pain in the posterior gluteal region over the sciatic notch. At the same time he developed a limp of the left leg. Six months later the pain had extended down to the inner aspect

of the left knee. The left leg became weak and there was considerable muscle atrophy of the lower left extremity. During the 6 months preceding admission there was constant pain involving the left hip and the upper portion of the left thigh. There was moderate obstipation and 40 pounds loss in weight. On admission, examination revealed a large firm mass palpable in the lower left quadrant. There was considerable muscle atrophy of the left lower extremity. The motion of the extremity at the hip was limited in all directions. There was diminished pain to touch over the distribution of the left second and third lumbar segments with motor loss and atrophy of the abductors and of the flexors of the thigh. The left knee jerk was absent. Roentgen examination of the pelvis showed an extensive lesion of the bone involving the left ilium, ischium, and inferior pubic ramus. There was expansion of bone; moderate areas of bone destruction; periosteal thickening; and new bone formation. The appearance was strongly suggestive of osteogenic sarcoma. Radio-strontium (582 μc.) was administered intravenously September 3, 1941. A biopsy was performed September 9, 1941.

Tissues were assayed with the following results:

Tissue	Radio-strontium uptake, μc./gm.	%/gm. tissue of dose
Bone tumor	0.483	0.082
Subcutaneous tissue and fascia (involved)	0.098	0.0016
Muscle	0.0124	0.0021
Skin	0.0086	0.0014
Fat	?	

CASE 6. [redacted] a 21-year-old white male (weight unknown), was admitted to the University Hospital August 4, 1941. Seven months prior to admission the patient was struck by a heavy piece of metal which produced an ecchymotic area over the outer aspect of the right thigh and which seemed of no consequence. About 2 months later a slight swelling was observed. At the same time a pain developed in the region of the right thigh, but this was not severe enough to incapacitate him. One month prior to admission the pain became more intense. An operation was performed and an encapsulated tumor was removed. This was diagnosed as myxo-fibro-osteosarcoma. Physical examination on admission revealed a firm, somewhat tender mass measuring approximately 10 cm. in diameter, directly above the incision resulting from the previous operation. On palpation the mass could not be clearly demarcated from the surrounding tissues. There was no evidence of inguinal metastasis. Roentgen examination revealed no metastasis to the parenchyma of the lungs, but examination of the upper

TABLE 1.—UPTAKE OF RADIO-STRONTIUM—MICROCURIES PER GM. AND % OF DOSE PER GM.—TISSUE—WET WEIGHT

	Case 1. [redacted]	Case 2.* [redacted]	Case 3. [redacted]	Case 4. [redacted]	Case 5. [redacted]	Case 6. [redacted]
Normal bone: μc./gm.	0.244	0.0131	0.0542	a. 0.0320 b. 0.0244	..	0.078
% dose/gm.	0.016	0.0011	0.015	a. 0.0098 b. 0.0070	..	0.012
Infiltrated bone: μc./gm.	0.0498	0.0073	a. 0.1401 b. 0.1586			
% dose/gm.	0.034	0.0006	a. 0.041 b. 0.044			
Tumor: μc./gm.	0.0361	..	0.0996	a. 0.0106 b. 0.0122	0.0483	0.388
% dose/gm.	0.0240	..	0.0279	a. 0.0032 b. 0.0033	0.082	0.090
Skin: μc./gm.	0.342	0.0064	0.0772	trace	0.0086	
% dose/gm.	0.022	0.0005	0.0216	..	0.0014	
Muscle: μc./gm.	0.1475	0.0036	0.0052	trace	0.0124	0.0005
% dose/gm.	0.010	0.0003	0.0014	..	0.0021	0.0007
Fat: μc./gm.	0.0066	0.0036	0.0002	trace	?	
% dose/gm.	0.0004	0.0003	0.0005			

* The short interval between administration of radio-strontium and amputation (12 hours) together with the fact that the radio-strontium was given orally probably accounts for the small uptake in all tissues.

right thigh showed a soft tumor mass in the upper portion of the thigh just below the trochanteric line. There was also an irregular area of calcification measuring approximately 6 by 3 cm. which was lateral and slightly posterior to the shaft of the femur. It appeared to have no connection with the femoral shaft. Radio-strontium (650 μc.) was administered intravenously August 2, 1941. An operation was performed August 6, 1941, and a tumor measuring 5 by 4 by 3 cm. was removed together with the surrounding muscle. There was no histologic evidence of malignant tumor in these tissues.

Tissues were assayed with the following results:

Tissue	Radio-strontium uptake, μc./gm.	%/gm. tissue of dose
Bone (uninvolved)	0.078	0.012
Tumor	0.588	0.090
Muscle	0.005	0.0007

Discussion. Despite the marked difference in the uptake of radio-strontium by various tissues, there is ample evidence that the maximum occurs in bone and tumor tissues. In soft tissues variation is especially noticeable, but a somewhat striking concentration is observed in several of the cases in the skin. This has suggested the desirability of investigating the rôle of the skin in strontium metabolism. Such studies are now in progress in this laboratory. It is noteworthy that different parts of the tumor show marked differences in the uptake of strontium. This might be due (apart from causes such as vascularization, regressive local changes, and so on) to difference in the metabolic rate in different parts of the tumor, depending on the state of cell development at the time of biopsy. The high uptake of strontium in areas where new bone is being laid down, whether this be normal or neoplastic, indicates that radioactive strontium will provide a valuable tool in the study of bone healing after experimental fractures. As with radioactive phosphorus in the case of new soft tissue cells, the rate of the laying down of new bone cells can be determined with labelled or radioactive strontium.

In order to evaluate the radiation effects of large doses of radio-strontium and to compare them with the effects of external sources of radiation such as Roentgen rays, it is desirable to attempt to convert the radiation emitted by radio-strontium into *r* units. This can be estimated from the energy of the emitted particles. Radio-strontium emits beta rays. Its half life is 55 days and its mean average life is 79.6 days. The maximum energy of radiation is 1.5 MEV. The particles from radioactive substances, however, have different energies (continuous spectrum); therefore, the mean energy values must be taken into calculations. For radio-strontium this is 0.75 MEV. According to this energy per particle: *One microcurie of radio-strontium yields 38 r units daily per gram of tissue,* assuming uniform distribution. However, strontium is taken up mainly by osseous tissue, so that the radiation is concentrated chiefly in bones and osteogenic cells.

It would appear from the foregoing that indications exist for the experimental therapeutic use of radio-strontium in cases of certain bone tumors. Particularly this would appear to be justified in view of the exceedingly bad prognosis in such cases, and because of the meagre resources which now exist for their treatment. Because of the known high resistance of bone neoplasms to radiation, experience may prove that radio-strontium has therapeutic value chiefly as an adjunct to external radiation (Roentgen rays, radium, neutrons), as a means of increasing total radiation to the affected areas.

Pursuant to these ideas, radio-strontium is now being applied therapeutically in several of the cases here reported and in several patients suffering from skeletal prostatic metastases. Later publications will describe these clinical studies.

Summary and Conclusions. 1. Investigations concerning the metabolism of calcium and strontium by means of their inert and radioactive forms have been reviewed.

2. Preliminary clinical studies with radioactive strontium in breast and prostatic carcinoma with bone metastases are reported.

3. Administration of radioactive strontium to 6 cases of bone tumor prior to biopsy or amputation shows uptake chiefly by growing bone and by osteogenic tumor tissue.

4. Various considerations seem to justify the therapeutic use of radioactive strontium in certain bone tumors. Clinical studies along this line are now in progress and will be reported at a later date.

We wish to express our appreciation to the staff of the Radiation Laboratory, and particularly to Dr. Martin Kamen, for generous coöperation in supplying radioactive strontium used in this study. We are indebted to Dr. Joseph Hamilton for the autoradiograph shown in Figure 1, and we wish to thank Drs. Leroy Abbott, Keene Haldeman and other members of the Department of Orthopedic Surgery of the University of California Hospital for permitting us to carry on these studies on their patients.

REFERENCES

1. Erf, L. A., and Pecher, C.: Proc. Soc. Exp. Biol. and Med., 45, 762, 1940.
2. Jones, H. B., Chaikoff, I. L., and Lawrence, J. H.: Am. J. Cancer, 40, 235, 1940.
3. Lawrence, E. O., and Cooksey, D.: Physiol. Rev., 50, 1131, 1936.
4. Lehnerdt, F.: Beitr. z. path. Anat. u. z. Allg. Path., 46, 468, 1909; 47, 215, 1910.
5. McCollum, E. V.: The Newer Knowledge of Nutrition, New York, The Macmillan Company, p. 274, 1939.
6. Pecher, C.: (a) Proc. Soc. Exp. Biol. and Med., 46, 86, 1941; (b) Preliminary Report on the Use of Radioactive Strontium in the Treatment of Metastatic Bone Cancer (in press).
7. Pecher, C., and Pecher, J.: Proc. Soc. Exp. Biol. and Med., 46, 91, 1941.
8. Stewart, D. W., Lawson, J. L., and Cork, J. M.: Physiol. Rev., 52, 901, 1937.
9. Stoeltzner, H.: Biochem. Ztschr., 12, 118, 1908.
10. Woodard, H. Q., and Higinbotham, N. L.: J. Am. Med. Assn., 116, 1621, 1941.